## Functional brain networks in multiple sclerosis: linking structural pathology to clinical disability

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# SUMMARY

The aim of the present dissertation was to test the hypothesis if clinical disability in MS could be explained by disruption of functional brain networks, and subsequently if this disruption of functional brain networks was related to structural pathology in MS.

In order to investigate the role of functional network topology as a link between structural pathology and clinical disability, there is a need for theoretical framework to understand the link between structure and function under healthy physiological conditions. When such a framework is established, the resulting principles can be applied to MS functional and structural network data. In the first two chapters this framework was investigated. In **chapter 2** a computational modelling study was performed where the applicability of neural mass models for realistic conditions was studied. The rationale is that neural mass models can be used for simulating MEG-like oscillations and functional networks and thus can be used to study pathological alterations of functional networks in MS. In this study it was investigated if conventional neural mass models, based on mean-field approximations, were able to capture the underlying dynamics of a neuronal population when the underlying homogeneity of such populations, as assumed in mean-field approximations, was violated. It was demonstrated that neural mass models were able to capture the mean activity of a neuronal population only under the specific conditions of dense connectivity among neurons in the population and a network size which was well beyond 100 neurons. When these conditions were met, then neurons in the neuronal population were able to synchronize, which led to a smaller contribution of signals with higher frequencies to the mean signal of the population. The mean activity of neuronal populations that contain little of higher frequencies could be captured by conventional neural mass models, as these act as low pass filters and therefore model signals which were dominated by lower frequencies.

In **chapter 3** another part of our theoretical framework was investigated. The aim was to study the presence of modality invariant functional connections in relationship to the underlying structural network. In order to quantify these modality invariant connections both fMRI and MEG were used. A modality-invariant functional core network in temporo-posterior regions including the precuneus was reported. This modality-invariant network was found for several MEG frequency bands. Secondly, it was found that this temporo-posterior core network emerged near a modality invariant phase transition for functional connectivity. Thirdly, it was demonstrated that this modality-invariant network was not merely reflection of the connections of the structural network, but more shaped by other properties of the structural network. A simple distance vs degree model was used, consisting of a weighted sum of the distance, defined as Euclidean distance between nodes, and the product of the degrees for any two nodes in the structural network. This simple analytical model was able to explain 12% of the variance for MEG and 33% of the variance for fMRI obtained functional networks. Adding the unweighted structural network in the model did not result in significant better predictions for both modalities.

In **chapter 4** the use of the minimum spanning tree (MST, an acyclic sub-network) for characterising brain network topology was investigated. The rationale behind this study was that conventional network metrics that aim to characterize the topology of brain networks are biased by properties of the network that are not related to the topology, such as network density, average network connectivity and network size. Therefore use of these metrics could lead to incorrect or incomplete descriptions of network topology. Three fundamental research questions were studied: 1) Are MST results insensitive for biases due to differences in network density or average connectivity? 2) Is MST topology also a good reflection of the topology of the original network? 3) How robust are these MST findings? These questions were investigated by simulating small-world and scale-free networks and it was found that in contrast to conventional measures, the MST is insensitive for differences in network density or average connectivity. Secondly, a rewiring procedure for both scale-free and small-world networks was executed that gradually changed these networks into random networks. The change in topology of the MSTs during this rewiring process was in the same direction as for the original networks. This indicates that MST topology can indeed be considered as a good reflection of the topology of the underlying network as it includes the set of links that show similar topology as the original network. Lastly, the strongest links in the MST were reordered to test the robustness of the MST and it was found that these near MST spanning trees were highly similar to the MST.

In **chapter 5** it was investigated if local resting-state oscillatory brain activity in MS patients could explain the presence of clinical disability (physical disability and cognitive dysfunction). MEG time-series were both recorded in MS patients and healthy subjects and it was found that there was slowing of oscillatory activity towards lower frequencies in MS patients. Results showed less power in the alpha2 band and more power in the alpha1 band in early MS patients, which had clinical relevance as this was related to worse cognitive performance and specifically to lower information processing speed in MS patients. Regional analysis revealed that this slowing predominantly occurred in temporo-posterior regions.

In **chapter 6** the attention was shifted from the power of MEG time-series to the phase relationships between these MEG-time-series in the same population as our power study described in chapter 5. Firstly, it was investigated if functional connectivity patterns in MS were altered due to the disease. Secondly, it was investigated if these alterations in functional connectivity were related to clinical disability and thalamic atrophy (a strong predictor for clinical disability). In this context, both whole brain functional connectivity and literature based resting state networks (RSN) were analysed. Whole brain analyses revealed lower functional connectivity in the alpha2 band and higher functional connectivity in the beta band in MS patients. These findings were replicated using a RSN approach. However, functional connectivity within RSN showed stronger correlations with clinical disability than whole brain functional connectivity, which indicates that these RSNs may consist of important connections that are more involved in cognitive processes. Particularly, modulations in the default mode network in MS patients were strongly associated with both physical

disability and cognitive status in MS. In addition, it was found that lower functional connectivity in the visual RSN was related to thalamic atrophy.

Hitherto, only local activity and the strength of functional connectivity were studied in MS patients. However, by merely analyzing these properties one may miss crucial information contained in the topology or organization of these functional connections as transferring information over networks is highly dependent on their topologies. In **chapter 7** it was investigated if MS patients showed alterations in network topology and whether these changes in network topology were related to clinical disability. For this purpose, the MST was computed as it was demonstrated in chapter 4 that it is capable of overcoming methodological biases with regard to arbitrary thresholds, average connectivity and density effects. Using empirical data from MEG recordings it was demonstrated that the MSTs of MS patients were characterized by a shift towards a more path-like topology in the alpha2 band, i.e. a less integrated network. Furthermore, a shift towards a more path-like network topology corresponded to a clinical disability in MS patients, and to be more specific to worse cognitive performance in MS patients. Finally, the distribution of the weights in the original network for both MS patients and healthy subjects corresponded to a shift towards a "*strong disorder*" regime, i.e. the distribution can be described by a power distribution where the exponent tends to go to zero, indicating that most of the traffic in the network takes place on the MST.

Since it was demonstrated that in MS patients functional networks were characterized by less integration, in **chapter 8**, the aim was to investigate the relationship between these functional network alterations and structural networks in MS. Structural co-variance networks were obtained from cortical thickness correlations and functional networks from MEG recordings. For this study, a new and larger patient cohort was studied where MS patients had relatively long disease duration. For both type of networks, both MST metrics and conventional metrics were computed. Again, functional networks in MS were characterized by less integration in terms of the MST in the alpha2 band, i.e. there was a shift towards a path-like topology. Furthermore, conventional network analysis revealed that there was a shift towards a more random or regular functional network topology depending on the frequency band for MS patients. However, for the structural co-variance networks only a shift towards a more regular network topology was found. This shift was also found for functional networks in the theta band in MS patients in contrast to the alpha2 band which showed a more random network topology. Further analysis revealed that structural-covariance between two regions was positively associated with functional connectivity between two regions in especially the theta band in MS patients. Importantly, these associations were not found when correlations between regional thickness of a region and the average functional connectivity of that region were computed. These findings indicate that functional connectivity changes in MS cannot be simply explained by regional gray matter atrophy itself but only if coordinated patterns of gray matter atrophy were taken into account.

In **chapter 9**, the relationship between functional networks in MS and structural pathology was investigated and more specifically, the role of thalamic atrophy for explaining disruption of cortical

functional networks. The rationale behind this approach is that thalamic atrophy is considered to be one of the best predictors for clinical disability. As the thalamus has a central role in the brain as a relay station and even as a structure that allows for parallel cortico-thalamo-cortical routes, thalamic atrophy could be associated with disruption of cortical functional networks leading to clinical disability. In this chapter a multi-modal MEG/fMRI approach was chosen where both MEG and fMRI data were used to construct cortical functional networks. In addition, fMRI was used to compute thalamo-cortical functional connectivity. Just as in our previous study the topology of cortical functional networks was analysed by using an MST approach and by computing conventional metrics. Analysis in this chapter firstly revealed thalamic atrophy in MS patients. Secondly, it was again demonstrated that functional networks in MS were characterized by a more path-like topology in terms of the MST in several frequency bands, but especially in the alpha2 band. This shift towards a more path-like cortical functional network topology was associated with thalamic atrophy as well as higher thalamo-cortical functional connectivity (fMRI) in MS patients. These findings suggest that there is a thalamo-cortical loop consisting of the thalamus, thalamo-cortical connections and cortico-cortical connections which is affected in MS. Importantly, disruption of this thalamo-cortical system was associated with clinical disability (physical disability and cognitive impairment).

Finally the main conclusions are:

1. Neural mass models can be used to mimic oscillations originating from neuronal populations and are a good approximation of the mean activity of a neuronal population if neurons in the underlying populations synchronize.
2. There is a functional temporo-posterior core network that emerged near a modality invariant phase transition for functional connectivity and which could be predicted by especially the degree product between nodes in the underlying structural network.
3. The MST is a robust sub-network that is insensitive for network density and average connectivity effects when comparing networks and at the same time its topology is representative for the topology of the underlying network.
4. There is slowing of resting state activity in MS which is also accompanied by higher functional connectivity in especially the default mode resting state network, which were both related to worse clinical outcome in MS.
5. Changes in functional connectivity in MS can better be explained by gray matter thickness if coordinated or correlated patterns of gray matter atrophy were taken into account.
6. Functional networks in MS are consistently characterized by less integrated topology in terms of the MST. This less integrated topology is consistently associated with worse clinical outcome and thalamic atrophy/pathology.